REMARKS

The Office Action has rejected Claims 15-22, 25, 26, 29 and 30 under 35 U.S.C. §103 as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 4,224,526 to Matsumoto ("Matsumoto") in view of the teachings in WO 97/48397, to which Beidermann et al. are inventors ("Beidermann et al.").

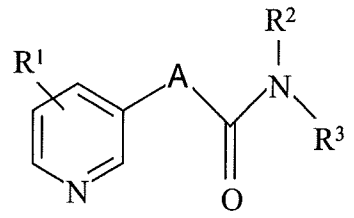
Applicants have amended the claims which when considered with the comments herein are deemed to place the present case in condition for allowance. Favorable action is respectfully requested.

At the outset, it is to be noted that Claims 1 *et seq.* have been amended to be directed to a method of reducing VEGF production. Support thereof is found throughout the specification. See for example Page 2, Line 23 to Page 3, Line 25 of the instant specification. Claim 26 is directed to a method of inhibiting or reducing angiogenesis by inhibiting or reducing VEGF production. Support thereof is found on Page 11, Line 27 to Page 12, Line 24 of the instant specification.

No new matter is added to the application.

In support of the rejection of Claims 15-22, 25, 26, 29 and 30 under 35 U.S.C. §103, the Office Action cites Matsumoto in view of Beidermann et al.

The present application is directed to, *inter alia*, inhibiting or reducing VEGF production in a mammal comprising administering to said mammal an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof:



I

wherein:

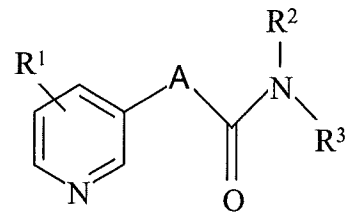
A is selected from the group consisting of the group members C_{1-10}-alkylene, C_{2-10}-alkenylene, and C_{2-10}-alkinylene, which group members may be optionally substituted by one, two or three groups independently selected from C_{1-3}-alkyl, fluoro, chioro, and bromo;

R^1 is selected from hydrogen, C_{1-6}-alkyl, fluoro, chloro, bromo, and perfluoro-C_{1-3}-alkyl;

R^2 is selected from hydrogen, C_{1-6}-alkyl, and C_{2-6}-alkenyl; and

R^3 is selected from the group consisting of the group members C_{1-6}-alkyl, (C_{5-8}-cycloalkyl)-C_{1-6}-alkyl, (C_{5-8}-heterocyclyl)-C_{1-6}-alkyl, C_{1-6}-alkyl (C_{5-8}-heterocyclyl)-C_{1-6}-alkyl, and C_{1-5}-alkylcarbonyl (C_{5-8}-heterocyclyl)-C_{1-6}-alkyl, which group members may be optionally substituted by one, two or three groups independently selected from C_{1-6}-alkyl, fluoro, chloro, bromo, oxo, perfluoro-C_{1-3}-alkyl, aryl, arylcarbonyl, heteroaryl, heteroarylcarbonyl, C_{5-8}-cycloalkyl and C_{5-8}-heterocyclyl.

In another embodiment the present invention is directed to a method of inhibiting or reducing angiogenesis by inhibiting or reducing VEGF production, said method comprising administering to said mammal an effective amount of a compound of Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein

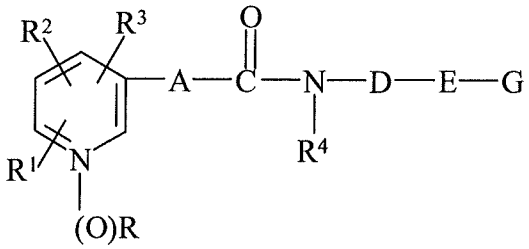
A is selected from the group consisting of the group members C_{1-10}-alkylene, C_{2-10}-alkenylene, and C_{2-10}-alkinylene, which group members may be optionally substituted by one, two or three groups independently selected from C_{1-3}-alkyl, fluoro, chloro, and bromo;

R^1 is selected from hydrogen, C_{1-6}-alkyl, fluoro, chloro, bromo, and perfluoro-C_{1-3}-alkyl;

R^2 is selected from hydrogen, C_{1-6}-alkyl, and C_{2-6}-alkenyl; and

R^3 is selected from the group consisting of the group members C_{1-6}-alkyl, (C_{5-8}-cycloalkyl)-C_{1-6}-alkyl, (C_{5-8}-heterocyclyl)-C_{1-6}-alkyl, C_{1-6}-alkyl (C_{5-8}-heterocyclyl)-C_{1-6}-alkyl, and C_{1-5}-alkylcarbonyl (C_{5-8}-heterocyclyl)-C_{1-6}-alkyl, which group members may be optionally substituted by one, two or three groups independently selected from C_{1-6}-alkyl, fluoro, chloro, bromo, oxo, perfluoro-C_{1-3}-alkyl, aryl, arylcarbonyl, heteroaryl, heteroarylcarbonyl, C_{5-8}-cycloalkyl and C_{5-8}-heterocyclyl.

Matsumoto is directed to 2-aryl-1H-perimidines as immunosuppressant agents. Beidermann et al. is directed to the use of pharmaceutically effective compounds of the formula



for the treatment of, *inter alia*, tumors or for immunosuppression.

The Office Action alleges that Matsumoto teaches that immunosuppressive agents are "used to treat or suppress mammalian immune response as a means of treating the autoimmune disease rheumatoid arthritis", referring to Claims 1 and 9. See Page 3 of Office Action. It also refers to Example 27, wherein it alleges that in Example 27, Matsumoto teaches rheumatoid arthritis is an inflammatory disorder where reduction of inflammation is a marker of immunosuppressive activity. The Office Action cites Beidermann et al., alleging that it discloses on Page 82, compound 259, a compound which it alleges falls within the scope of the present claims. It also alleges that Beidermann et al. disclose that this compound therein is also an immunosuppressant agent.

According to the Office Action, it would be obvious to use the compounds of the Beidermann et al. for treating rheumatoid arthritis because of the commonality of the compounds in both references having the utility of an immunosuppressant.

However, Matsumoto do not teach, disclose or suggest the use of the compounds therein for inhibiting or reducing VEGF production. In addition, Matsumoto does not teach, disclose or suggest the method of inhibiting or reducing angiogenesis by inhibiting or reducing VEGF production. A review of Matsumoto clearly reveals that there is no mention of VEGF inhibitors therein or its use in inhibiting or reducing VEGF production. Further, a review of

Matsumoto clearly reveals that there is no mention of angiogenesis - - let alone a means of reducing or inhibiting angiogenesis by inhibiting or reducing VEGF production, as claimed.

The teachings in Beidermann et al. do not overcome the inadequacies of Matsumoto et al. Again a review of Biedermann et al. clearly reveals that there is no mention therein of the use of the compounds therein for inhibiting or reducing VEGF production or of inhibiting or reducing angegenesis by inhibiting or reducing VEGF production. In fact nowhere in the document are the terms "VEGF" or "angiogenesis" ever mentioned.

Since neither Matsumoto nor Beidermann et al. teach, disclose or suggest the use of the compounds of Formula I herein for inhibiting or reducing VEGF production or, for inhibiting or reducing angiogenesis by inhibiting or reducing VEGF production, the combination cannot teach, disclose or suggest this utility.

Thus, for the reasons provided this rejection under 35 U.S.C. § 103(a) is obviated; withdrawal thereof is respectfully requested.

Therefore, in view of the Amendment to the Claims and the Remarks hereinabove, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully Submitted,

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